What Is a Virus?

2

Abstract

Viruses are built from short sequences of nucleic acid, either DNA or RNA wrapped in a protein shell. Until the invention of the electron microscope, it was impossible to visualize a virus. The first viruses to be visualized were bacteriophage, which appeared to have a head and tail-like structure. Only the nucleic acid entered the bacterial cell through the tail. Animal viruses were described as spherical or rod-shaped; they were bound to receptors and were taken up by the cell. After the crystallization of the tobacco mosaic virus, there was much discussion as to whether viruses were "living" organisms; the controversy continues to this day. Although viruses were defined in part on the basis of size and filterability, viruses much larger than the traditional viruses have recently been isolated. Studies of viral replication indicate that most viruses self-assemble as a result of interactions between the viral proteins to form a viral capsid that interacts with the nucleic acid to form the whole. The viral replication cycle and synthesis is presented in this chapter. Viral classification into a Linnaean scheme has been proposed, but newer methods using nucleic acid homologies are changing classification. Viruses are spread in the human population by various means, including airborne particles, fecal-oral contact, clothing, insects, and contact with other animals (zoonosis).

2.1 Definition of a Virus

Although viruses tend to be diverse in terms of the diseases they cause and the organs they attack, all viruses have a unity of structure and consist of proteins and nucleic acid. Some viruses are also encased in a lipid membranous envelope (Fig. 2.1). Their mode of replication is not binary (one divides into two, two divide into four, etc.), as in most other organisms, but occurs as a burst of thousands of virus particles from a single virus over a short time. The number of viruses

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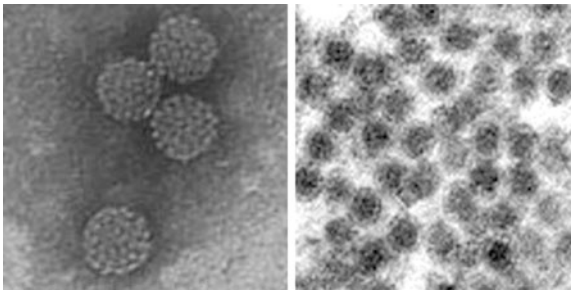

Fig. 2.1 Papilloma virus-16 and dengue virus (ICTVdB picture gallery with permission). Dengue virus is an enveloped virus

produced in cell culture or the blood is in the tens of millions per milliliter of media or blood. This mode of replication alone makes viruses unique. All other life forms contain DNA as genetic material and RNA as a message or intermediate for the formation of proteins or other structures. Viruses are also unique in that they contain either RNA or DNA as the genetic material. To date, no virus has been discovered that contains both types of nucleic acid as genetic material, although both types are used during virus replication in the cell. Viruses do not contain ribosomes, mitochondria or other cell-like organelles, and are thus completely parasitic. Since they cannot replicate without the metabolic processes of the host cell, they are genetic parasites. This differentiates viruses from bacteria or other single-cell microorganisms (e.g., protozoa), most of which can replicate in culture on their own, although they can also be parasitic. One other feature distinguishing viruses from other organisms in general is their small size and ability to pass through filters. This was certainly a major criterion in the early days of virology, although large viruses have recently been discovered. Viruses were not retained by filters made from diatomaceous earth (*kieselguhr*), extensively used at the beginning of the twentieth century. This characteristic was originally used as the major characteristic in differentiating a virus from bacteria, fungus or protozoa.

André Lwoff, a French microbiologist (who studied *lysogeny*, which is the insertion of bacteriophage DNA into the chromosome of a host), defined a virus in negative terms, using the following characteristics [1]:

- Possessing only one type of nucleic acid.
- Multiplying in the form of their genetic material, i.e., either RNA or DNA. This is not strictly true, since hepatitis B virus is a DNA virus but replicates as an RNA intermediate. Retroviruses are RNA viruses but replicate through a DNA.
- Unable to undergo binary fission and
- Lacking an energy system, including mitochondria and ribosomes.

This is a negative definition, and stresses the **non-cellular** nature of viruses. Fundamentally, then, a virus is a package of genetic information protected by a protein shell for delivery into a host cell to be expressed and replicated. The virus eventually takes over the cell completely for its own replication and in the process may kill (lyse) the cell or, in the case of tumor viruses, can permanently alter the cell [2].

Fig. 2.2 First electron microscope as invented by Ruska and Knoll (Wikipedia)

It was impossible to define a virus in terms of shape or physical characteristics until one could be seen; this had to await the development of the electron microscope. In 1931, two German scientists, Ernst Ruska and Max Knoll, invented the electron microscope (Fig. 2.2). This was a great improvement over the light microscope and allowed one to actually "see" viruses. One major disadvantage, however, is that the preparation for visualizing material by EM may distort the specimen because viable material cannot be used. The EM, as it became, uses electrons speeded up in a vacuum, aimed at the specimen, and gives an outline of the structure on an electron-sensitive photographic plate. Ernst Ruska later moved to the Siemens Company in Germany, where the first commercial electron microscope was developed. He received the Nobel Prize in Physics in 1986.

2.2 Are Viruses Alive?

Since the crystallization of viruses in 1935, there has been controversy as to whether viruses are alive or inanimate. The best analogy is to that of a seed. Is a bean seed alive? It has the properties of life under certain circumstances, but can be kept in an inert state for years. As soon as it is planted under appropriate conditions, it becomes "alive." A virus differs in that it cannot reproduce unless it is in a host cell. Thus, one may think of the virus as the bean and the host cell as the soil. Viruses use the metabolism of the host cell, although there are large viruses, such as smallpox, that carry genes similar to those of the host cell, which

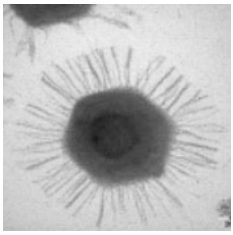

Fig. 2.3 Micrograph of Mimivirus (ICTVdB)

code for metabolic enzymes, and some genes mimic those of the host cell and thus disrupt cellular metabolism by acting as decoys. These viral products are termed virokines. However, even such viruses cannot multiply on their own since they need cellular components for their replication and protein synthetic apparatus. Where did those mimicking genes come from? Were these genes derived from the host cell since they mimic host functions and interfere with these functions, or were they acquired by the host eons ago from the virus? (This is a controversial and open question). Thus the virus is at the edge of life, and can exist in two states—an inert state and a living state.

In 2004, a large virus (Mimivirus) was discovered in a strain of amoeba, [3]. It is considered and called a virus since it cannot replicate outside its host, and although it carries genes for many metabolic functions, it does not code for ribosomal genes, making it dependent on the host cell for protein synthesis. It is as large as many bacteria, but despite this, it seems to be another example of an entity at the boundary between living and inert forms. One has to consider a continuum from the inert chemical (organic chemical) to more complex ones with the ability to reproduce, which then gives life. The definition of life or living is an arbitrary one (see Chap. 4 on bacteriophage), and is defined in different ways by different scientists and philosophers. The discovery of the Mimivirus has given rise to the discussion as to whether this is an ancestor of other viruses or is the result of genes breaking away from the host and becoming independent. An electron micrograph of Mimivirus is shown in Fig. 2.3, and a schematic in Fig. 2.4.

This virus has an icosahedral capsid of 400 nm in diameter and 125 nm long closely packed fibers projecting out from the capsid surface (750 nm total length). The capsid contains the internal core surrounded by an internal lipid layer. A fivefold axis displays a starfish-shaped structure.

2.3 Viral Structure

Viruses come in two main shapes as seen from electron micrographs: spherical, or rod-shaped. Some viruses are naked, while others have a lipid envelope around them, often derived from the host cell (see Fig. 2.1).

In some cases, viruses approach the shape of regular solids. In some of these viruses, 20 replicas of the same proteins make up the capsid. This can be a single protein, or three or many proteins, which interact spontaneously when in contact

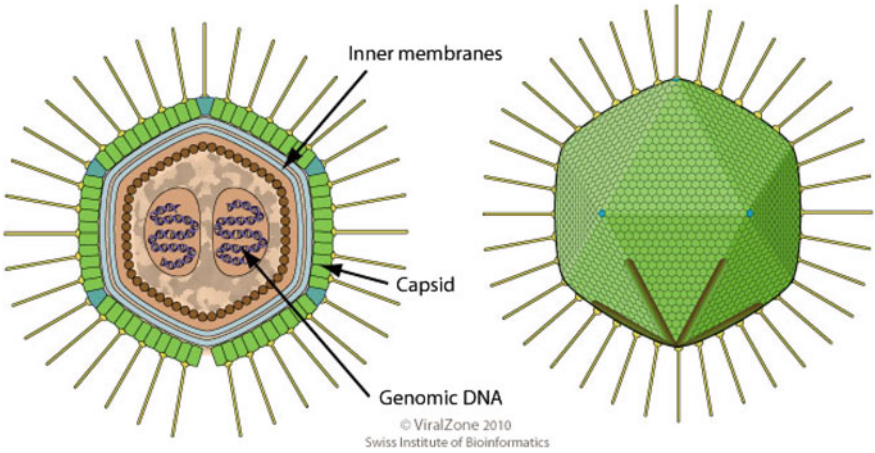

Fig. 2.4 Mimivirus structure (ViralZone, SIB Swiss Institute of Bioinformatics, with permission)

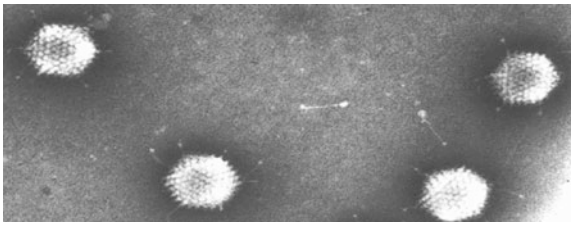

Fig. 2.5 Structure of adenovirus. Note peplomers (spikes) from vertices and free peplomer (ICTVdB picture gallery)

through template domains at their edges. The bonds between the capsid proteins are angled so that the complete structure acquires the form of a regular icosahedron.

Figures 2.1, 2.4, 2.5 and 2.6 illustrate the basic shape of icosahedral viruses.

Spherical viruses exist in two classes: non-enveloped but may have attachments to the vertices (corners) of the icosahedron (see figure of adenovirus); or enveloped.

All mammalian living cells are covered by a membrane—the viability of the cell depends on the integrity of this membrane. Enveloped viruses leaving the cell must, therefore, allow this membrane to remain intact if the cell is to survive, or even if the cell eventually dies. This is achieved by the budding of the viral nucleo-capsid through the membrane, during which the virus becomes coated in a lipid envelope derived from the host cell membrane or modified membrane (see Fig. 2.7, 2.8).

Some viruses are rod-shaped, as illustrated by the tobacco mosaic virus (TMV) and vesicular stomatitis virus (VSV). In the case of TMV this rod is made up of repeating units of a single coat protein enclosing the nucleic acid in Fig. 2.9.

Since viruses utilize the same protein repeatedly for their structure, they require very few genes. In order to replicate, they need genes to code for their coat protein and replication. Thus many viruses, such as poliovirus, may contain only enough nucleic acid for 5–6 genes. In some cases, the same nucleic acid codes for different

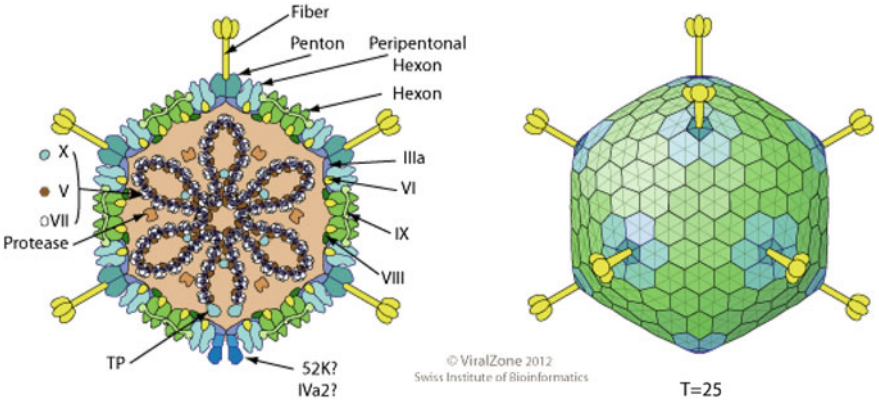

Fig. 2.6 Schematic of adenovirus structure showing icosahedral proteins and peplomers (spikes) (Courtesy of ViralZone, SIB Swiss Institute of Bioinformatics)

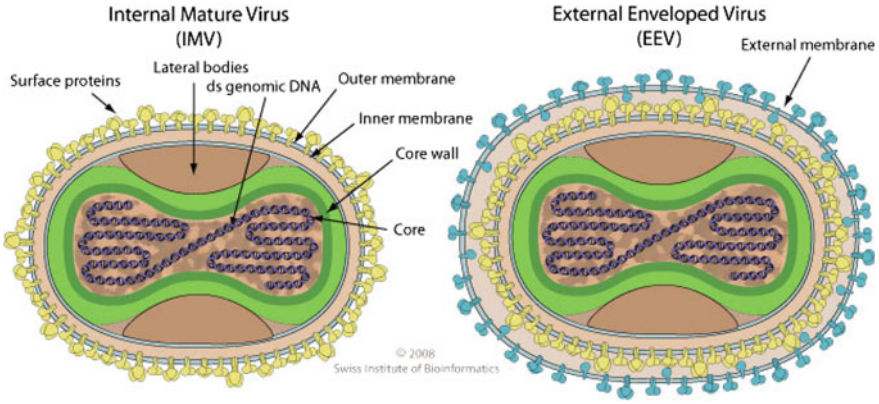

Fig. 2.7 Enveloped virus, such as poxvirus (vaccinia) (ViralZone, SIB Swiss Institute of Bioinformatics)

proteins by starting "read-out" at various locations on the nucleic strand, or using both strands of DNA.

In most cases, viruses undergo self-assembly. Apart from a few bacteriophages in which a scaffolding protein exists, viral proteins interact with each other or with the nucleic acid almost as if they have magnetic properties to spontaneously form a stable structure. The ability to undergo self-assembly is influenced by both pH (acidity or basic conditions) and salt concentrations. Poliovirus capsids will undergo self-assembly in the test tube from sub-viral particles. Classical experiments have shown that mixing RNA of Holmes' ribgrass virus and the tobacco mosaic virus protein will give rise to a viable virus. The species propagated will depend on the source of the RNA, in this case, RNA from Holmes' ribgrass virus [4].

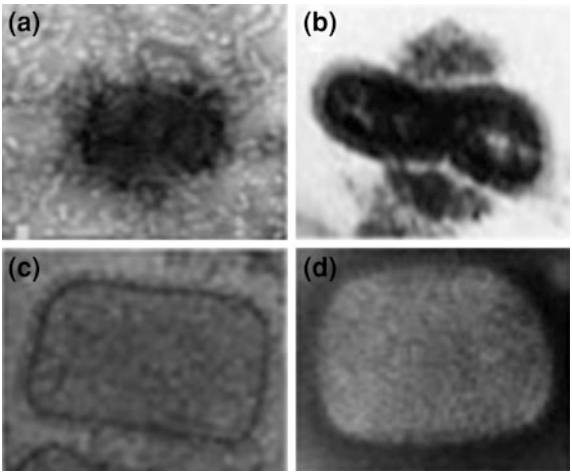

Fig. 2.8 Enveloped poxvirus (**a**) and removal of membrane by detergent and reducing agent. Note inner core remains (**b**) (ViralZone, SIB Swiss Institute of Bioinformatics)

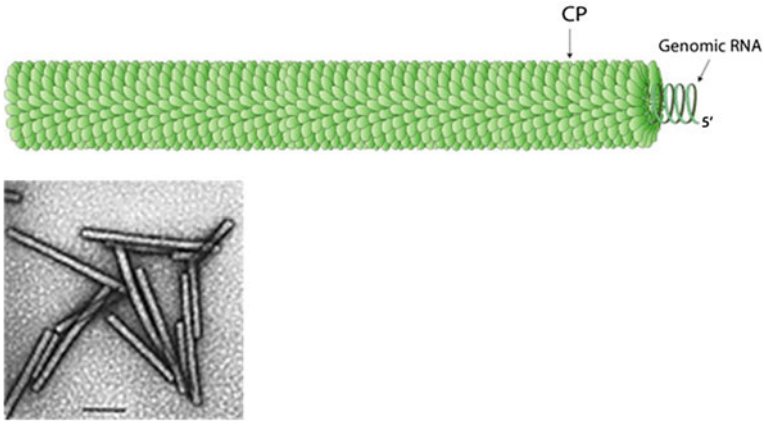

Fig. 2.9 Tobacco mosaic virus (ViralZone, SIB Swiss Institute of Bioinformatics. and ICTVdB). Non-enveloped, rigid helical rods with a helical symmetry. Virion is about 18 nm in diameter, and 300–310 nm in length

The ability to undergo self-assembly makes it easy to reconstruct viruses in the test tube, and has been done for polio and other viruses. Figure 2.10 illustrates the self-assembly of the hepatitis B capsid.

Thus viruses are small particles containing only a few genes that succeed in controlling the host's protein-synthesizing machinery to make more virus. Outside the living cell, they are completely inert and can only be seen at high resolution via electron microscopy.

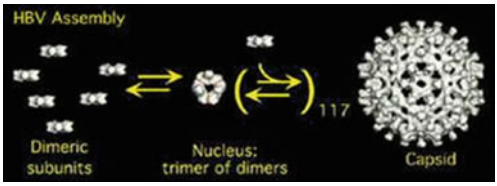

Fig. 2.10 Self-assembly of hepatitis B virus (courtesy of A. Zlotnick, Indiana University)

2.4 Nucleic Acid

Two types of nucleic acid exist in nature—DNA and RNA. In humans, as in all replicating organisms (*archaea*, *bacteria* and *eukaryotes*) the genes that make up the chromosomes are strands of DNA. Viruses contain either RNA or DNA as their genetic material. DNA in most organisms is a double-stranded structure, based on Watson and Crick pairing; however, in viruses, DNA and RNA can be either single-stranded or double-stranded. Since the viral genome is small, consisting in many cases of just a few genes—some of which code for enzymes involved in replication—there is a limited amount of genetic material.

The single virus is referred to as the "virion." It consists of an outer shell (protein capsid, or membrane), the function of which is to protect the genetic information from physical, chemical, or enzymatic damage, and a nucleocapsid containing the genetic information and any required replicating enzymes. The outer surface of the virus is also responsible for recognition of and attachment to the host cell. Initially, this takes the form of binding of a virus-attachment protein to a cellular receptor molecule. One can imagine this as a key and lock mechanism. Once the virus attaches to the cell, it is engulfed through the cellular membrane and the viral coat removed in small cellular vesicles, releasing the viral nucleic acid into the cytoplasm for replication (Fig. 2.11). In the case of bacteriophage, the viral coat is not taken into the cell, but the genetic material is injected into the bacterial cell as if through a syringe, with the bacteriophage proteins remaining attached through their tails.

2.5 Virus Classification

The common names of viruses are associated in many cases with the place the virus was first isolated (e.g., Ebola is the location in the Congo where the disease was first recognized); the organ from which the virus is isolated (e.g., adenovirus from the adenoids); the symptoms of the virus (pox virus, yellow fever); or, finally, with the names of the persons isolating and identifying the virus (e.g., Epstein-Barr). Using the symptoms caused by a virus can lead to confusion. There are many viruses that cause what we generally call hepatitis. For example, the *picornavirus* hepatitis A causes common jaundice, a self-limiting disease; hepatitis B causes serum hepatitis associated with blood transfusions; and hepatitis C,

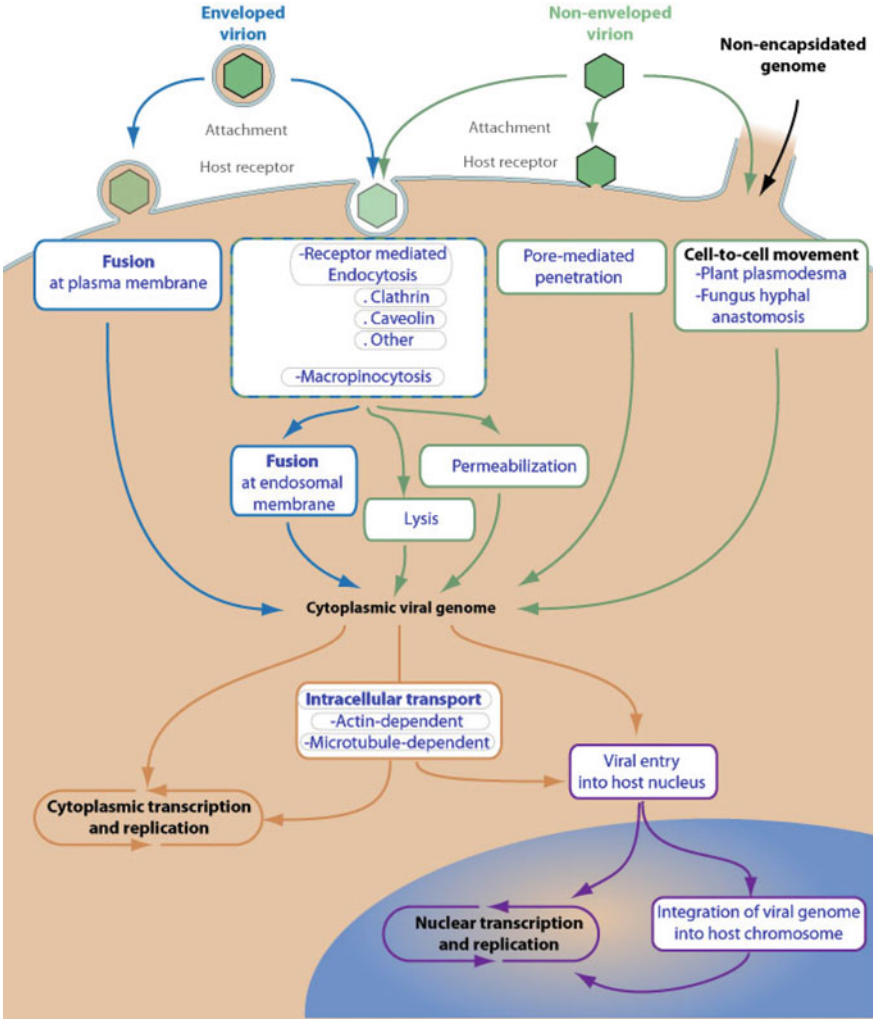

Fig. 2.11 Mode of attachment and uptake of virus into the mammalian cell. Note the difference between enveloped and non-enveloped virus (ViralZone, SIB Swiss Institute of Bioinformatics)

a *flavivirus*, transmitted in blood and blood products, eventually causing liver cirrhosis and liver cancer.

Many attempts have been made to classify viruses, following the classical scheme of Linnaeus, the eminent Swedish botanist. However, since viruses are quite invisible, and we know them from either the diseases they cause or from their shape in electron micrographs, it has been very difficult to relate them to each other. Newer methods of classification depend on the molecular structure of the virus, type of nucleic acid, and mode of replication. More accurate methods in DNA

and RNA sequencing allow for virus classification based on sequence homology. The relationship between and among viruses is constantly being revised, based on sequence data.

2.6 Virus Replication Cycle

At the molecular level, the infection of a single cell with a virus can result in the synthesis of thousands of virus particles. When a virus kills a cell in culture, it is referred to as a lytic infection and in the whole organism, such as a human as an acute infection. Examples of this type of infection are poliovirus, the common cold virus (*rhinovirus*), and smallpox. Such viruses either "kill" the host or are eventually controlled by the immune system and are thus self-limiting.

Some viruses persist for a long period of time, giving rise to chronic infections. We do not know why this happens, since in many cases the components of the immune system appear to be functioning normally. It is possible that the virus has the ability to "dampen" the activity of the immune system or the first lines of defense against infection, such as interferon. This seems to be the case with a virus such as hepatitis C, which is able to knock out the interferon system (at least in cultured cells) and possibly also interfere with immune cell activity in vivo, thus allowing for the persistence of the virus.

Other viruses can integrate into the host genome, resulting in cell transformation or tumor formation. Such viruses interfere with the cell cycle and cell replication. Cervical cancer is caused by a papilloma virus, which alters the cell cycle to its advantage. HIV integrates into the human chromosome, making it impossible to eradicate completely. Other viruses, such as the herpes viruses, establish a long-lasting infection, but they also have an acute phase, the formation of cold sores in or near the mouth, or genital lesions, and a latent stage in which the virus "hides" in neurons, either in the soma or in axons. Chickenpox, also a herpes-like virus, can remain dormant for years, and then erupt as shingles, usually when the immune system is compromised, for example during cancer chemotherapy, or during AIDS infection.

The typical virus life cycle is as follows: The virus interacts with its target cell and introduces its nucleic acid into the cell. The interaction occurs through the binding of the virus to a unique receptor domain on the cell membrane (Fig. 2.11). This receptor is a normal component of the cell and may have other functions. Virus proteins are made and modify the host cell metabolism so that host proteins are no longer made, or the host cell replication cycle is affected. All of this is to allow the virus to produce more of itself, thus diverting cell metabolism to virus production. The viral proteins are produced in one part of the cell, the replicated nucleic acid in another, and somehow they find each other, interact, and form virus particles that are expelled from the cell. These viruses then infect nearby cells. Immediately after infection in vivo, the body reacts by producing interferon and

other immune enhancing molecules known as cytokines, which are the first line of defense against the virus; this response is called "innate immunity." Adaptive immunity, the production of antibodies for a specific virus, will not occur until much later (10–21 days). Symptoms usually occur a few days after infection, although during this asymptomatic period a person may be infectious. This is particularly true in the case of viruses such as HIV, where obvious symptoms may not occur for quite some time (The role of the immune response is discussed in detail in Chap. 6).

2.7 How Are Viruses Spread?

In discussing the mode of viral transmission, one must consider the tissue or organ tropism of the virus. Viruses bind to receptor sites on the cells of specific tissue. It is the presence of these receptor sites that make an animal or cell susceptible to the virus. The virus contains unique proteins, occasionally as surface projectiles that interact specifically with the receptors. Thus some viruses, such as hepatitis virus, attack the liver and no other tissue. Other viruses, such as the common cold virus (rhinovirus), have adapted to cooler body temperatures and infect the lining of the nose, which is cooler than the rest of the body. Mutations in a receptor—or lack thereof—can lead to resistance to virus infection. Individuals lacking specific chemokine receptor sites, such as CXCR4 and CCR5, are resistant to HIV infection due to the inability of the virus to bind to cells lacking these receptors.

Scientists divide the mode of virus spread into two categories—direct contact and indirect contact. Direct contact includes blood-borne transmission, fecal-oral transmission, airborne spread by droplets or aerosol, contact with bedding, clothes, etc. (fomites), and vector (usually mosquitoes or other insects) [5]. Indirect contact spread includes cases where mucus from a runny nose may get onto the hands, or virus may be left on a surface such as a doorknob, telephone, or countertops, and is picked up by a second individual, who then touches his eyes or nose, resulting in infection. For example, cytomegalovirus (a virus of the herpes class) can be transmitted between children if one child drools on a toy and a second child picks it up and then put his hands in his mouth or eyes. Viruses can be transmitted in droplets; however. the area covered is not very large, usually only a few feet depending on the size of the droplets.

(The exception may be in planes, where the virus droplets may persist and spread in the dry closed confinement.) An example of common vehicle transmission might be where a food contaminated with hepatitis A is consumed by many people who all become sick. Vector transmission is a very common means of transmission; the best studied cases include yellow fever, dengue virus, and West Nile fever—viruses all transmitted by mosquitoes.

The many modes by which viruses are transmitted are summarized in Table 2.1.

Table 2.1 Mode of transfer of viruses

Mode of transfer	Virus	Symptoms
Aerosol and airborne droplets	Rhinovirus, adenovirus, respiratory syncytial virus	Common cold: upper- and lower-tract respiratory infections
Fecal-oral	Poliovirus, hepatitis A, noroviruses	Diarrhea, vomiting, gastric pain
Insect transmission by mosquitoes	Dengue, yellow fever, West Nile fever	High fever, hemorrhagic fever, internal bleeding
Sexual transmission	HIV, HSV-2, herpes 8, hepatitis B, papilloma, EB virus	In case of HIV—immunodeficiency. Kaposi's sarcoma. Others: warts, blisters on genitals and anus
Blood-borne diseases (excluding insects): dirty needles and blood transfusions	Hepatitis C, hepatitis B, HIV	Hepatocellular carcinoma
Routes unknown or mixed: transmitted from other animals (zoonoses)	SARS, MERS, Ebola, Lassa fever, Nipah, hantavirus	Very fatal infections. Usually internal bleeding

2.8 Aerosol and Airborne Spread

In studying the spread of respiratory viruses, scientists have concentrated on respiratory syncytial virus (RSV), influenza, and rhinoviruses, the three viruses most commonly found in homes, old age homes, institutions and schools. RSV is the most common respiratory infection in children worldwide. Attendance at daycare center ensures that a child will be infected with RSV during the first few years of life, and infection results in 0.05–1 % of children being hospitalized with bronchitis.

Although it would be expected that transmission of RSV would be by airborne particles, this does not appear to be the case. Transmission takes place by contact, both direct and indirect. In experiments designed by Hall et al. [6] highly symptomatic infants who were producing abundant secretions were placed in cribs. Three categories of nurse volunteers were brought into the room. "Cuddlers" played with the infant, changed his or her diaper and performed other routine care. "Touchers" did not touch the baby but had extensive contact with the child's environment, which had been heavily contaminated with secretions. "Sitters" sat next to the crib reading a book for 3 h but did not touch anything in the immediate environment. Five of the seven "cuddlers," four of ten "touchers" and not one of 14 "sitters" developed RSV infection. Thus transmission did not appear to be airborne, since none of the nurses sitting beside the children was infected. The other nurses were infected either by direct contact with the child, or from secretions that were on the crib or other objects handled by the child. Children with

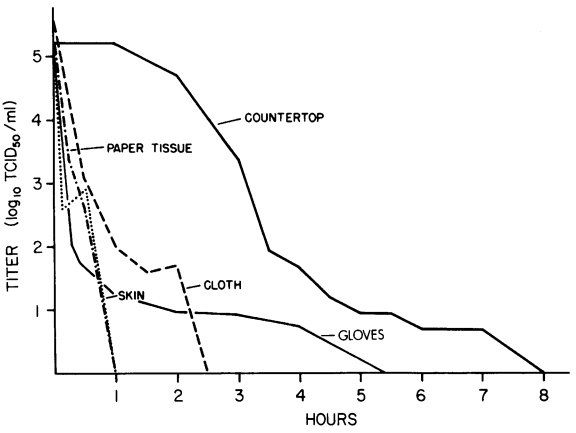

Fig. 2.12 Mean titer and duration of recovery of respiratory syncytial virus (*RSV*) from skin (hands) and four environmental surfaces that were contaminated with RSV in both medium and pooled normal adult nasal secretion [6]

RSV secrete large amounts of virus, which can be viable for up to 7 h on tabletops or other surfaces (Fig. 2.12).

RSV is often spread in hospitals (nosocomial spread) through lack of thorough hand-washing after handling infected children. It is important that all surfaces be washed down with an effective antiviral compound after exposure to children with RSV. Detergents containing alcohol are effective in destroying RSV, and anyone in contact with this infection should wear gloves as a barrier to infection.

Rhinoviruses follow a similar pattern. A 2007 study [7] showed that sick people leave cold viruses on the things they touch, such as door handles, pens and light switches. Adults with naturally acquired rhinovirus colds have been found to contaminate 35 % of environmental surfaces in hotel rooms after overnight occupancy, using reverse transcriptase-polymerase chain reaction (RTPCR) to detect viral RNA. In addition, viral RNA on surfaces (light switch, phone button, and telephone handset) could be transferred to fingertips during activities of daily life. Although RTPCR measures viral RNA contamination, parallel experiments testing for growth of virus in cell culture resulted in similar results. Virus could be found on these objects for as long as 18 h. There are, however, two conflicting sets of data on how rhinoviruses are spread, one maintaining that the virus is predominantly spread by indirect contact through nasal secretions, the other that the major mode of transmission is through aerosol. Studies at the University of Wisconsin have shown that when individuals with a cold are kept in the same room with uninfected individuals, the virus does spread by aerosol, but not as fast as expected. It may take hours of exposure for others to contract the cold. However, in these experiments, virus was not detectable on game chips, suggesting that in the case of contact infection, there is a need for large amounts of fresh secretion [8]. Thus, again, hand-washing should be effective against the spread of this virus.

In the last few weeks of spring 2009, pictures from around the world appeared in the press and on television of people wearing facemasks to prevent the spread of *influenza* (H1N1). Influenza is predominantly spread by droplets that may travel as

far as six feet and from surfaces contaminated from nasal secretions. Adults can spread the virus 1 day before becoming sick and up to 7 days after the infection begins. Children can spread the virus for a longer time.

To avoid the spread of the virus, people should stay away from the sick and stay home if sick. It also is important to wash hands often with soap and water; if not available, use an alcohol-based hand rub. Linens, eating utensils, and dishes belonging to those who are sick should not be shared without thoroughly washing them. Eating utensils can be washed either in a dishwasher or by hand with soap and water, and do not need to be cleaned separately. Furthermore, frequently touched surfaces should be cleaned and disinfected at home, at work and at school, especially if someone is ill (http://www.cdc.gov/flu/about/disease/spread.htmCDC).

Secondary infections with pneumonia often occur during an influenza epidemic. During a normal outbreak, influenza targets the elderly. There have been epidemics in which younger members of society are targeted, and the great pandemic of 1918 attacked mostly 20- to 30-year-olds. Experiments indicate that the influenza virus may remain active on various surfaces for a few days, depending on the type of surface. Influenza virus spread can be inhibited to some extent by the use of surgical masks.

2.9 Fecal-Oral Spread

The most prevalent virus spread by this means is the Norwalk (norovirus). These viruses have been in the news recently due to infections that have occurred on cruise ships. The Norwalk virus was named for Norwalk, Ohio, where there was an outbreak in the 1970s. Since there are many species of norovirus, this is now the officially accepted name. This stomach virus ranks second (behind the common cold) in the occurrence of viral illnesses in the United States. The centers for disease control (CDC) reported over 267 million cases of diarrhea in 2000, and estimates about 5–17 % of these may have been caused by a norovirus. Cruise ships are not the only place where one can pick up this nasty bug; of the 348 outbreaks reported to the CDC between 1996 and 2000, only 10 % were in vacation settings. Restaurants, nursing homes, hospitals, and daycare centers are the most likely places to pick up a norovirus infection. Symptoms of norovirus illness usually begin about 24–48 h after exposure to the virus, but they can appear as early as 12 h after ingestion of contaminated food. People infected with norovirus are contagious from the moment they begin feeling ill until at least 3 days after recovery. Some people may be contagious for as long as 2 weeks. Therefore, it is particularly important for people to practice good hand-washing after having recently recovered from a norovirus. The major source of contamination is leafy greens such as lettuce, fresh fruit and shell fish. The most important precautions against norovirus are hand-washing, laundering of contaminated clothing and blankets, and cooking shellfish to high temperatures.

Another virus spread by this means, from diarrhea and vomiting, is rotavirus. This virus occurs predominantly in children, although there have been outbreaks in adults. It also occurs suddenly with an outbreak of fever, vomiting, and stomach cramps, and usually last a few days. At one time it was the leading cause of death of young children in the U.S. Since the advent of a vaccine in 2005, its seriousness has decreased. Prior to 2005, almost all children in the U.S. were infected with rotavirus before their fifth birthday. In the pre-vaccine period, rotavirus was responsible for more than 400,000 doctor visits; more than 200,000 emergency room visits; 55,000–70,000 hospitalizations; and 20–60 deaths in children younger than 5 years of age (CDC). Many other viruses, such as polio, are spread through the fecal-oral route and are discussed separately.

2.10 Insect Route

Dengue virus is a leading cause of illness and death in the tropics and subtropics. As many as 400 million people are infected annually by dengue virus, which is caused by any one of four related viruses transmitted by mosquitoes. There is no vaccine to prevent infection with dengue virus, and the most effective protective measure is to avoid mosquito bites. When infected, early recognition and prompt supportive treatment can substantially lower the risk of medical complications and death.

An estimated 2.5 billion people live in over 100 endemic countries and areas where dengue viruses can be transmitted. Up to 50 million infections occur annually, with 500,000 cases of dengue hemorrhagic fever and 22,000 deaths—mainly among children. Prior to 1970, only nine countries had experienced cases of dengue hemorrhagic fever (DHF); since then, the number has increased more than fourfold and continues to rise (see map in Fig. 2.13) (World Heath Organization).

During the nineteenth century, dengue was considered a disease that sporadically caused epidemics at long intervals, a reflection of the slow pace of transport and limited travel at that time. Dengue has emerged as a worldwide problem since the 1950s, and in the last 50 years, the incidence has increased 30-fold. Although dengue is rarely found in the continental United States, it is endemic in Puerto Rico and in many popular tourist destinations in Latin America, Southeast Asia and the Pacific islands (Fig. 2.14).

The reason for the increase in epidemic dengue fever has been the lack of eradication of mosquitoes (*Aedes aegypti*). With populations moving from the country to urban areas, there is now a large non-immune population available to the infected mosquitoes. There has been, over time, an increase in the use of plastic containers, which are breeding grounds for mosquito larvae. As has also been shown for yellow fever (see Chap. 10), the availability of old tires filled with rainwater is also a locale for breeding. Air travel has helped spread the mosquito from continent to continent and as a carrier of the disease.

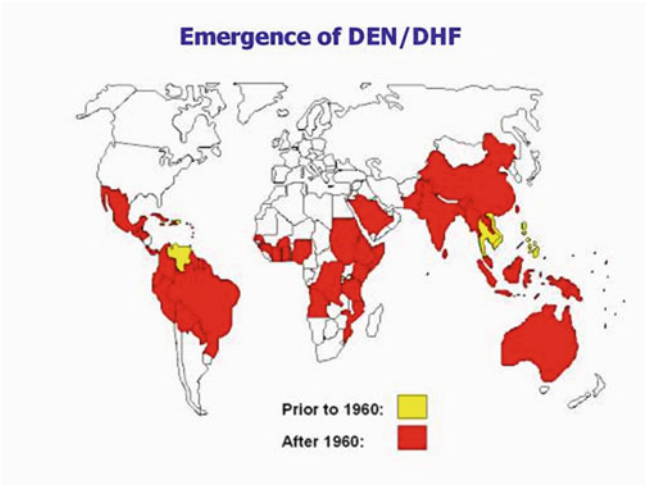

Fig. 2.13 Range of dengue fever infection in the world. Note increase in area after 1960 (World Health Organization)

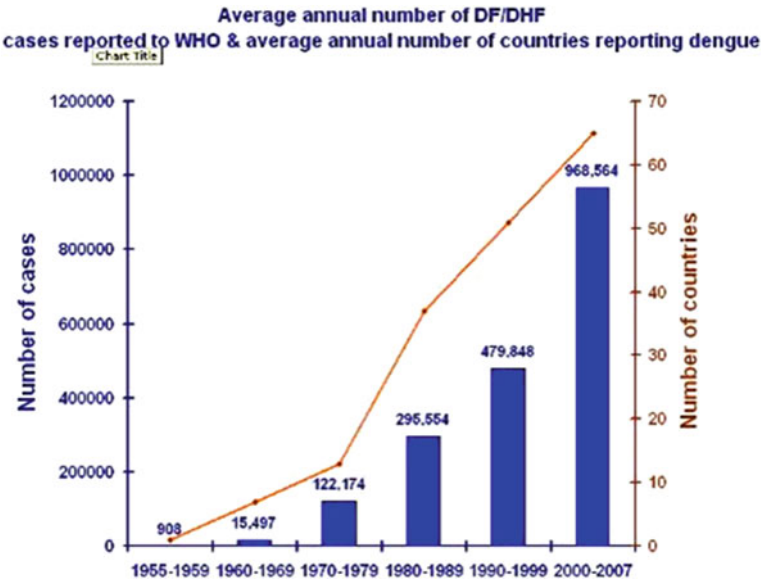

Fig. 2.14 Increase in cases of dengue fever and dengue hemorrhagic fever from 1955–2007 (World Health Organization)

As in the case of other diseases spread by mosquitoes, the virus replicates in the gut of the insect, and then accumulates in the salivary gland waiting to be transmitted at the next meal. The extrinsic period (time in the insect before becoming

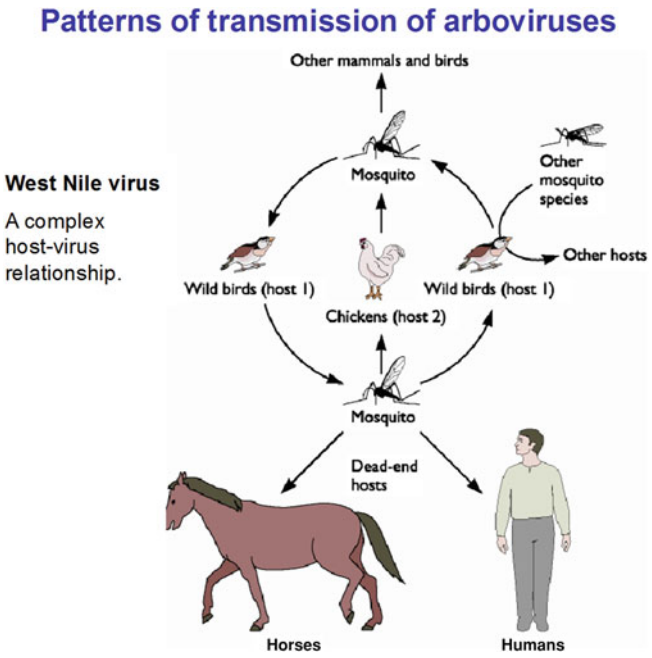

Fig. 2.15 Example of "dead end" infection. Main target of virus/vector is the *bird*; *man* and *horses* are accidental targets

infectious) is approximately 7 days. There is a similar pattern of infection for the yellow fever virus.

West Nile Virus is among the most common mosquito-borne viruses in the U.S., and there is currently no vaccine for it. Only about 20 % of those bitten by virus-loaded mosquitoes develop fever, body aches, headache, and nausea. Another 1 % develop neurological problems that can be serious. Humans are a "dead-end" host for the virus, in that it is not transmitted further. The virus is predominantly found in birds (see http://www.cdc.gov/westnile/resources/pdfs/Bird%20Species%201999-2012.pdf), which lists those species in which the virus is found (Fig. 2.15).

2.11 Sexual Transmission

A large number of viruses can be transmitted sexually. These include Herpes simplex 2, HIV, hepatitis B and papilloma viruses. The mode of transmission is the same in all these cases, and depends on the level of promiscuity, irrespective of whether the sex is heterosexual or homosexual. All can be prevented by the use of condoms or by limiting the number of partners. One of the major problems with

the sexually transmitted disease is that in many cases the infected individual does not realize that he or she has the infection. Each of these viruses is discussed separately in later chapters.

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